PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN P. WHITE
COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10112
UNITED STATES OF AMERICA

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	21 APR 1995
Applicant's or agent's file reference 43016-A-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US94/00757	21 JANUARY 1994	22 JANUARY 1993

Applicant
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Julie Krsek-Staples
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 43016-A-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US94/00757	International filing date *(day/month/year)* 21 JANUARY 1994	Priority date *(day/month/year)* 22 JANUARY 1993
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 45/05, 31/70; A01N 43/08 and US Cl.: 424/277.1; 514/25		
Applicant SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 AUGUST 1994	30 MARCH 1995
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Julie Krsek-Staples Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US94/00757

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-143 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-43 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-26 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US94/00757

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-43	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-43	NO
Industrial Applicability (IA)	Claims	1-43	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990).

Livingston et al disclose a vaccine administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (p 7046-7048). Livingston et al teach that the vaccine is administered at a concentrations of 100, 200, or 300 μg with an adjuvant, *Bacillus* Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046 column 1 paragraph 3 and paragraph bridging p 7046 and 7047). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination (p 1074 paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies that IgG antibodies to the GM2 (p 7047 paragraph bridging columns 1 and 2). Livingston et al also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas (p 7045, column 1 paragraph 2). Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). Livingston et al also do not teach the use of any other gangliosides in a vaccine preparation.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1). Ritter et al discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. Livingston et al (U.S. Pat 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1 lines 22-28). Ritter et al (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic that GD3 (abstract).

It would have been obvious to one of ordinary skill in the art (Continued on Supplemental Sheet.)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 7 and 43 are objected to because they are duplicate claims.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description of the invention does not satisfy PCT Article 5 in that the invention must be disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

The description discloses antibodies generated as a result of administration of a ganglioside GM2 vaccine are associated with a favorable prognosis in patients with melanoma. The description does not teach that vaccines using GM2 or other gangliosides are able to prevent other forms of cancer. Bystryn teaches that for cancer immunotherapy to be effective the immune responses induced must be directed to antigens being expressed by the tumor being treated. Bystryn discloses the pattern of tumor antigens expressed by cancers of the same histological type in different individuals is variable. Bystryn also teaches that there is variation in the pattern of tumor antigens expressed by different tumor cells of the same histological type in the same individual (p 84 paragraph 1). Furthermore, the profile of tumor antigens expressed by a tumor during its progression may be altered by the immune response of the host as a result of antigenic modulation. Bystryn also discloses that as a consequence of this variability it is unlikely that vaccines prepared from a single tumor antigen will be effective against a broad range of tumors of the same histological type and for the same reason autologous vaccines may not be effective against other tumor cells in the same patient (p 84, column 1). Therefore, due to the variability of tumor antigens both within an individual and among different individuals, it is unpredictable whether the claimed gangliosides would be effective in treating other forms of cancer.

The description teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines.The description does not provide guidance on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. As described in the description (p 19) the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. Due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides.

Claims 1-43 are objected to under PCT Article 6 because they are not fully supported by the disclosure for the reasons set forth above.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
to modify the vaccine taught by Livingston et al by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages taught above by Ritter et al (1991). It would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston et al (U.S. Pat 5,102,663) and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. It would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990), and would be expected to produce and enhanced antibody response compared to GD3. It would have been obvious to optimize the concentration of the oligosaccharide in the vaccine composition because such optimization constitutes routine experimentation and is within the skill of the ordinary artisan.

Claims 4, 13-17 and 35 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. at 5,102,663) and Ritter et al (1990) as applied to claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 above, and further in view of Kensil et al and Marciani et al.

The teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach the use of QS21 as an adjuvant.

Kensil et al teach that QS21 produced a higher antibody response that aluminum hydroxide (p 433, column 2, paragraph 4 and Fig. 3). Kensil et al also teach that the immune responses obtained with QS21 reached a plateau at doses between 10 and 80 μg in mice (p 433, column 1, paragraph 3). Marciani et al teach the use of QS21 as an adjuvant in a vaccine at concentrations of 10 and 20 μg (p 91, column 2, paragraph 4 and p 93, paragraph 1). Marciani et al also teach that the QS21 adjuvant did not cause a toxic reaction in cats (p 93, paragraph 1).

It would have been obvious to one of ordinary skill in the art to add QS21 as an adjuvant to the vaccine taught by the above cited art because QS21 produces a higher antibody response than the commonly used adjuvant, aluminum hydroxide, as taught by Kensil et al, and QS21 is not toxic to animals as taught by Marciani et al. It would also have been obvious to use doses of between 10 and 200 μg because the immune response obtained with QS21 plateaus at doses between 10 and 80 μg and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

Claims 22-25, 37 and 38 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) as applied to claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 above, and further in view of Irie et al.

The teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

Irie et al teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31). It would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

---------- NEW CITATIONS ----------

Cancer and Metastasis Reviews, Volume 9, issued 1990, J.C. Bystryn, "Tumor Vaccines", pages 81-91, see pages 83-84.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN P. WHITE
COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10112
UNITED STATES OF AMERICA

PCT

WRITTEN OPINION

(PCT Rule 66)

	Date of Mailing *(day/month/year)* JAN 23 1995
Applicant's or agent's file reference 43016-A-PCT	**REPLY DUE** within **ONE** months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US94/00757	21 JANUARY 1994	22 JANUARY 1993

International Patent Classification (IPC) or both national classification and IPC
IPC(6): A61K 45/05, 31/70; A01N 43/08 and US Cl.: 424/277.1; 514/25

Applicant
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[X]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22 MAY 1995.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Julie Krsek-Staples
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (January 1994)★

WRITTEN OPINION

International application No.
PCT/US94/00757

I. Basis of the opinion

1. This opinion has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

[X] the international application as originally filed.

[X] the description, pages 1-143 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.

[X] the claims, Nos. 1-43 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-26 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

3. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:
NONE

WRITTEN OPINION

International application No.
PCT/US94/00757

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-43	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-43	NO
Industrial Applicability (IA)	Claims	1-43	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Research) in view of Ritter et al (1991) and Livingston et al (U.S. Pat. 5,102,663) and Ritter et al (1990).

Livingston et al disclose a vaccine administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (p. 7046-7048). Livingston et al teach that the vaccine is administered at a concentrations of 100, 200, or 300 μg with an adjuvant, *Bacillus* Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p. 7046 column 1, paragraph 3 and paragraph bridging pp. 7046 and 7047). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination (p. 1074 paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies that IgG antibodies to the GM2 (p. 7047 paragraph bridging columns 1 and 2). Livingston et al also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas (p. 7045, column 1, paragraph 2). Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). Livingston et al also do not teach the use of any other gangliosides in a vaccine preparation.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p. 406, paragraph 1). Ritter et al discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. Livingston et al (U.S. Pat. 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28). Ritter et al (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic that GD3 (abstract).

It would have been obvious to one of ordinary skill in the art (Continued on Supplemental Sheet.)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 7 and 43 are objected to because they are duplicate claims.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description of the invention does not satisfy PCT Article 5 in that the invention must be disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

The description discloses antibodies generated as a result of administration of a ganglioside GM2 vaccine are associated with a favorable prognosis in patients with melanoma. The description does not teach that vaccines using GM2 or other gangliosides are able to prevent other forms of cancer. Bystryn teaches that for cancer immunotherapy to be effective the immune responses induced must be directed to antigens being expressed by the tumor being treated. Bystryn discloses the pattern of tumor antigens expressed by cancers of the same histological type in different individuals is variable. Bystryn also teaches that there is variation in the pattern of tumor antigens expressed by different tumor cells of the same histological type in the same individual (p. 84 paragraph 1). Furthermore, the profile of tumor antigens expressed by a tumor during its progression may be altered by the immune response of the host as a result of antigenic modulation. Bystryn also discloses that as a consequence of this variability it is unlikely that vaccines prepared from a single tumor antigen will be effective against a broad range of tumors of the same histological type and for the same reason autologous vaccines may not be effective against other tumor cells in the same patient (p. 84, column 1). Therefore, due to the variability of tumor antigens both within an individual and among different individuals, it is unpredictable whether the claimed gangliosides would be effective in treating other forms of cancer.

The description teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines.The description does not provide guidance on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. As described in the description (p. 19) the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. Due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides.

Claims 1-43 are objected to under PCT Article 6 because they are not fully supported by the disclosure for the reasons set forth above.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
to modify the vaccine taught by Livingston et al by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages taught above by Ritter et al (1991). It would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston et al (U.S. Pat. 5,102,663) and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. It would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990), and would be expected to produce and enhanced antibody response compared to GD3. It would have been obvious to optimize the concentration of the oligosaccharide in the vaccine composition because such optimization constitutes routine experimentation and is within the skill of the ordinary artisan.

Claims 4, 13-17 and 35 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Research) in view of Ritter et al (1991) and Livingston et al (U.S. Pat. 5,102,663) and Ritter et al (1990) as applied to claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 above, and further in view of Kensil et al and Marciani et al.

The teachings of Livingston et al (Cancer Research) and Ritter et al (1991) and Livingston et al (U.S. Pat. 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach the use of QS21 as an adjuvant.

Kensil et al teach that QS21 produced a higher antibody response that aluminum hydroxide (p. 433, column 2, paragraph 4 and Fig. 3). Kensil et al also teach that the immune responses obtained with QS21 reached a plateau at doses between 10 and 80 μg in mice (p. 433, column 1, paragraph 3). Marciani et al teach the use of QS21 as an adjuvant in a vaccine at concentrations of 10 and 20 μg (p. 91, column 2, paragraph 4 and p. 93, paragraph 1). Marciani et al also teach that the QS21 adjuvant did not cause a toxic reaction in cats (p. 93, paragraph 1).

It would have been obvious to one of ordinary skill in the art to add QS21 as an adjuvant to the vaccine taught by the above cited art because QS21 produces a higher antibody response than the commonly used adjuvant, aluminum hydroxide, as taught by Kensil et al, and QS21 is not toxic to animals as taught by Marciani et al. It would also have been obvious to use doses of between 10 and 200 μg because the immune response obtained with QS21 plateaus at doses between 10 and 80 μg and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

Claims 22-25, 37 and 38 lack an inventive step under PCT Article 33(3) as being obvious over Livingston et al (Cancer Research) in view of Ritter et al (1991) and Livingston et al (U.S. Pat. 5,102,663) and Ritter et al (1990) as applied to claims 1-3, 5-12, 18-21, 26-34, 36, and 39-43 above, and further in view of Irie et al.

The teachings of Livingston et al (Cancer Research) and Ritter et al (1991) and Livingston et al (U.S. Pat. 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

Irie et al teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31). It would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

---------- NEW CITATIONS ----------

Cancer and Metastasis Reviews, Volume 9, issued 1990, J.C. Bystryn, "Tumor Vaccines", pages 81-91, see pages 83-84.

SEARCH COPY

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No: PCT/US 94/00757

International Filing Date: 21 JAN 1994 (21.01.94)

Name of receiving Office and "PCT International Application": PCT INTERNATIONAL APPLICATION RO/US

Applicant's or agent's file reference (if desired) (12 characters maximum): 43016-A-PCT

Box No. I TITLE OF INVENTION

GANGLIOSIDE-KLH CONJUGATE VACCINES PLUS QS-21

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
1275 York Avenue
New York, New York 10021
United States of America

☐ This person is also inventor

Telephone No.: NONE

Facsimile No.: NONE

Teleprinter No.: NONE

State (i.e. country) of nationality: United States of America

State (i.e. country) of residence: United States of America

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LIVINGSTON, PHILIP O.
156 East 79th Street
Apartment 6C
New York, New York 10021
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below)

State (i.e. country) of nationality: United States of America

State (i.e. country) of residence: United States of America

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

HELLING, FRIEDHELM
303 East 71st Street
Apartment 6H
New York, New York 10021
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below)

State (i.e. country) of nationality: Germany

State (i.e. country) of residence: United States of America

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as [XX] agent [ ] common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WHITE, JOHN P.
Cooper & Dunham
30 Rockefeller Plaza
New York, New York 10112
United States of America

Telephone No
(212)977-9550

Facsimile No
(212)664-0525

Teleprinter No
422523 COOP UI

[ ] Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (*mark the applicable check-boxes; at least one must be marked*):

Regional Patent

[XX] EP **European Patent**: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

[ ] OA **OAPI Patent**: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Gabon, Guinea, Mali, Mauritania, Senegal, Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*) .....

National Patent (*if other kind of protection or treatment desired, specify on dotted line*):

[ ] AT Austria .....
[XX] AU Australia .....
[ ] BB Barbados
[ ] BG Bulgaria .....
[ ] BR Brazil .....
[XX] CA Canada
[ ] CH and LI Switzerland and Liechtenstein
[ ] CZ Czech Republic .....
[ ] DE Germany .....
[ ] DK Denmark .....
[ ] ES Spain .....
[XX] FI Finland
[ ] GB United Kingdom
[XX] HU Hungary .....
[XX] JP Japan .....
[ ] KP Democratic People's Republic of Korea .....
[XX] KR Republic of Korea .....
[ ] LK Sri Lanka
[ ] LU Luxembourg .....
[ ] MG Madagascar
[ ] MN Mongolia .....
[ ] MW Malawi .....
[ ] NL Netherlands
[XX] NO Norway
[XX] NZ New Zealand
[ ] PL Poland .....
[ ] PT Portugal .....
[ ] RO Romania
[XX] RU Russian Federation .....
[ ] SD Sudan
[ ] SE Sweden
[ ] SK Slovak Republic .....
[ ] UA Ukraine
[XX] US United States of America (continuation-in-part) .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

[ ] .....
[ ] .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.*)

PCT/US 94/00757

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
Item (1) United States of America	(22.01.93) 22 January 1993	08/009,268	
Item (2)			
Item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) Serial Number 08/009,268

Box No. VII EARLIER SEARCH

Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office):	Date (day/month/year):	Number:
United States of America	22 January 1993 (22.01.93)	08/009,268

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	4	sheets
2. description	143	sheets
3. claims	5	sheets
4. abstract	1	sheets
5. drawings	26	sheets
Total	179	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) identified in Box No. VI as item(s):
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other (specify): Assignment

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

BY: James S Quirk DATE: 1/21/94

NAME: Mr. James S. Quirk

TITLE: Senior Vice President

For receiving Office use only

1 Date of actual receipt of the purported international application:	62 Rec'd PCT/PTO 21 JAN 1994	2. Drawings ☐ received ☐ not received
3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4 Date of timely receipt of the required corrections under PCT Article 11(2):		
5 International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT/US 94/00757

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which or for which the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
Item 1: United States of America	22 January 1993	08/009,268	
Item 2:			
Item 3:			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): Serial Number 08/009,268

Box No. VII EARLIER SEARCH

Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office):	Date (day/month/year):	Number:
United States of America	22 January 1993	08/009,268

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1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
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5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other (specify): Assignment

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Philip D. Livingston MD — Philip D. Livingston — Date: 1/21/94

Friedhelm Helling — Friedhelm Helling — Date: 1/21/94

For receiving Office use only

1. Date of actual receipt of the purported international application: 62 Rec'd PCT/PTO 21 JAN 1994
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

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Date of receipt of the record copy by the International Bureau:

This sheet is part of and does not count as a sheet of the national application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No. PCT/US 94 / 00757

Date stamp of the receiving Office 21 JAN 1994

Applicant's or agent's file reference 43016-A-PCT

Applicant

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . $200.00 [T] — 200
2. SEARCH FEE . . . . . $410.00 [S] — 410

International search to be carried out by RO/US

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 179 sheets.

first 30 sheets . . . . . $530.00 [$b_1$] — 530

149 (remaining sheets) x $10.00 (additional amount) = $1,490.00 [$b_2$] — 1490

Add amounts entered at b_1 and b_2 and enter total at B . . . . . $ 2,020.00 [B] — 2020

Designation Fee

10 (number of designations) x $128.00 (amount of designation fee) = $ 1,280.00 [D] — 1280

(If that total exceeds the figure which corresponds to the amount of the designation fee multiplied by ten, enter the latter figure in box D.)

Add amounts entered at B and D and enter total at I . . . . . $ 3,300.00 [I] — 3300

4. FEE FOR PRIORITY DOCUMENT . . . . . ------- [P] — 12

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box . . . . . $ 3,910.00 TOTAL — 3922

☐ The designation fee is not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☒ cheque (for $3,910.00)	☐ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/US

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

03-3125	21 January 1994	Robert J. Cobert
Deposit Account Number	Date (day/month/year)	Signature Robert J. Cobert, Reg. No. 36,108

See Notes to the fee calculation sheet